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Why young people's substance use matters for global health

Wayne Hall¹, George Patton², Emily Stockings³, Megan Weier¹, Michael Lynskey⁴, Kate Morley⁴ and Louisa Degenhardt³

1. Centre for Youth Substance Abuse Research
University of Queensland
Brisbane QLD Australia 4078
2. Centre for Adolescent Health
Murdoch Children's Research Institute
Melbourne VIC Australia 3052
3. National Drug and Alcohol Research Centre
UNSW Australia
Sydney NSW Australia 2052
4. National Addiction Centre
Institute of Psychiatry, Psychology & Neuroscience, King's College London
London, United Kingdom

Corresponding author: Louisa Degenhardt

National Drug and Alcohol Research Centre, UNSW Australia, Sydney NSW 2052 Australia

Email: l.degenhardt@unsw.edu.au

Phone: +61 2 9385 0333

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Summary

Puberty shifts emotional regulation and increases risky behaviour, including substance use, when young people are completing their education, making a transition to employment, and forming longer term intimate relationships. This systematic review of reviews considers the potential effects of alcohol, tobacco and illicit drug use during this period on: 1) social, psychological and health outcomes in adolescence and young adulthood; 2) role transitions, and later health and social outcomes of regular substance use initiated in adolescence; and 3) the offspring of young people. We have looked for consistent support for causal relationships from different but complementary research designs and evidence of biological plausibility. Many adverse health and social outcomes have been associated with different types of substance use. The major challenge lies in deciding which are causal. There are also: qualitatively different harms associated with different substances; differences in the life stage at which these harms occur; and differences in the quality of evidence for different substances and health outcomes. The preponderance of evidence comes from a small number of high income countries so it is unclear whether the same social and health outcomes would occur in other countries and cultures. Nonetheless, enough harms are causally related to substance use in young people to warrant high quality research design interventions to prevent or ameliorate these harms.

Introduction

The social transitions that occur during adolescence and young adulthood (the period from ages 10-24 years) are critical for a young person's later life trajectories. As noted in **paper 1**¹ of this series, this period of life is also when substance use typically starts, and patterns of use become established.

The emotional shifts that accompany adolescence and young adulthood create opportunities and vulnerabilities.² The process of puberty changes physical development, shifts emotional regulation and increases risky behaviours, such as, drug use. These risks occur at a time when young people are completing their education, making a transition into employment, and forming longer term intimate relationships. These transitions may be disrupted by substance use and the development of substance use disorders which often first emerge during adolescence. They commonly co-occur with, and complicate the course of, common mental disorders that also emerge in adolescence and young adulthood.³

In this paper, we consider the potential effects of substance use during this period on: 1) social, psychological and health outcomes during adolescence and young adulthood (i.e. consequences of intoxication and regular use); 2) social and health outcomes during the life course (i.e. outcomes of role transitions, and later health and social outcomes of regular substance use which is initiated in adolescence and sustained over years or decades); and 3) the offspring of young people who use substances. We focus on the substances that are most commonly used in this period, namely, alcohol and tobacco, and illicit drugs, particularly cannabis, amphetamines, cocaine and opioids (as described in **paper 1**¹ in this series). Our search strategy is summarised in **panel 1** and in more detail in **webappendix A**.

Panel 1: Search strategy

Studies of the possible consequences of substance use in young people have been conducted almost entirely in high income countries. It is uncertain whether these consequences would be the same in: low and middle income countries; countries with very different cultures; and countries where the opportunities for young women differ markedly (see **Panel 2**). These are all important areas for future research.

Panel 2: Cross-national differences in impacts of substance use in young people

The uniqueness of adolescence and young adulthood

In the past 20 years researchers have realised that neurodevelopment extends into the second and third decades of life. This realisation has heightened concern about the neurobiological vulnerability of adolescents to the adverse effects of regular substance use on cognitive and emotional development.

Optimum cognitive abilities require healthy brain development. The primary motor and sensory areas (e.g. sensorimotor cortex and occipital pole) develop well before higher order brain centres involved in executive and emotional regulation. These processes are non-linear and show marked regional differences in the timing of synaptic growth and death.⁴ Cortical grey matter increases in volume in school age children. Cortical thinning then begins in the occipital and primary somatosensory cortex and continues into young adulthood as the prefrontal cortex matures.⁵ Brain white matter increases in volume and integrity in adolescence and young adulthood as connections form between the association cortices. Subcortical structures in the limbic system, including the amygdala and hippocampus, also increase in volume during adolescence.⁶

Social and cognitive development: adolescents are not “little adults”

In animals, puberty affects brain development; similar processes occur in humans.⁷ The clearest links in humans are with the maturation of subcortical structures involved in emotional processing: the amygdala, hippocampus and corpus striatum.^{8,9}

Puberty is also linked to changes in social and emotional processing,¹⁰ and there is increasing focus on social and emotional development in adolescence.¹¹ Social cognition - the ability to interpret the behaviour of peers and others – becomes more highly developed after puberty.¹² ¹³ Social cognition is central to good interpersonal functioning, mental health and well-being, educational attainment and, later, employment. In late childhood and adolescence, young people become especially sensitive to their social environments and to social cues. Experiences in this period may embed emotional and behavioural patterns.¹⁴ The prevalence of substance use in the young person's peer group may have a major effect on their own substance use (see discussion of peer networks below). In addition, the extent of substance use in family members, including parents, can increase the risk of use, although it is unclear to what extent this reflects genetic, social or environmental influences (or a combination of all of these).¹⁵

Studies have identified parts of the brain involved in social and emotional processing during adolescence. The dorsomedial prefrontal cortex is involved in understanding the emotional and mental states of others and in reflecting on one's status with one's peers (see below).¹² In functional magnetic resonance imaging (fMRI) studies, hormonal levels are associated with activity in cortical areas involved in socio-emotional processing, such as, anterior temporal cortex and medial prefrontal cortex.¹⁶ The temporo-parietal junction, the posterior temporal sulcus, and the anterior temporal cortex are central to the acquisition of the social and emotional skills required for adult functioning. This reflects cortical changes, but white matter changes are also required for impulse control.¹⁷

Cognitive skills, such as language and problem solving, are elaborated during adolescence and peak in the early to mid-20s.¹⁸ There is a growing capacity for sustained attention, extended working memory and increased inhibitory control of emotions, all of which facilitate goal-directed activities.¹⁹ Deficits in these cognitive skills are associated with a range of behavioural and emotional problems that emerge in late childhood and adolescence. The successful acquisition of these skills has long-term benefits for adult intellectual functioning, health and life expectancy.^{20, 21}

There is a range of studies that suggest that substance use during adolescence may have greater neuropsychological impact than substance use later in life,²² with some suggestion of a greater sensitivity to neurotoxic effects²³. Animal models have demonstrated that the adolescent brain is more vulnerable to the neurotoxic effects of substance use than the matured adult brain.²⁴ Studies of human adolescents have to date been dominated by cross-sectional study designs, making it harder to be confident the same effects occur in humans.

It is also important to consider the relative impact of the rapidly changing psychosocial and emotional environment faced during adolescence, and how this may increase adolescent vulnerability to substance initiation and dependence. Emerging evidence from adolescent humans has begun to identify that particular brain regions (namely the ventromedial prefrontal cortex and the left inferior frontal gyrus, areas associated with emotional) may be able to discriminate between future substance users and their non-using peers. Importantly however, these brain regions have a modest impact on substance use initiation when considered in isolation.²⁵ Other social and emotional developmental factors during this rapid period of development also appear to work in combination with neurobiological differences in predicting adolescent substance initiation.²⁵

The importance of peer context for adolescents

Adolescents' decisions differ from those of older adults in assigning greater weight to peer acceptance and peer influence.²⁶ Social and online media have dramatically extended the range of peer engagement in the time that young people may spend interacting with peers (see **Panel 3**).

Panel 3: Potential impacts of social media

The greater salience of peers is one reason why puberty is a risk period for substance use and problematic use.²⁷ As noted in **paper 1**¹, affiliation with peers who use substances is one of the strongest and most consistent correlates of a young person's substance use. If these associations do not reflect the influence of confounding covariates, there are two major explanations of this "peer-association" effect. Peer-**socialisation** theory posits that the behaviour of peers affects individuals' actions, whereas peer-**selection** theory proposes that an individuals' personality and substance use affects who they affiliate with²⁸. Evidence from longitudinal studies suggests that both effects may be in play.

Other factors may modify the influence of substance using peers.²⁸ Peer association has larger effects on substance use in adolescents who: are younger; mature early; and have higher social anxiety, sensation seeking, and popularity.²⁸ Peers have less impacts in those with more parental monitoring, more authoritative parenting and who spend more time with their families.²⁸

Changes in the structure of adolescence

One of the most marked changes in recent decades is lengthening of the period during which the social transitions of adolescence occur, especially in high income countries. Adolescence has typically been framed as starting at puberty and ending with adult' transitions into marriage and parenthood²⁹. In many developed countries the age of puberty has declined since early in the 19th Century³⁰. At the same time in these countries, and increasingly in low and middle income countries, marriage and parenthood are occurring later in young adult life.³¹ These changes have expanded the risk period for substance use. Substance use (and other health risk behaviours) decrease once marriage and parenthood occur³² (see also **paper 1**¹), so any delays in making these role transitions provide more time for heavier, riskier patterns of substance use to become entrenched, and to persist after delayed marriage and/or parenthood.

Assessing the effects of substance use in young people

The impacts of substance use in young people might differ from those in adults for several reasons (see **Panel 4**). These are related to the unique social, cognitive and physical changes that accompany adolescence and young adulthood that were highlighted earlier.

Panel 4: Why substance use in young people differs from substance use in older adults

There is a challenge in deciding which of the adverse outcomes associated with substance use are caused by it because many of the risk factors for substance use and these adverse outcomes are shared. This complicates the task of attributing specific adverse outcomes in young adulthood to adolescent substance use.

The research methods that can be used to address some of these challenges are summarised in **panel 5**. In general, when deciding whether a relationship is causal, we have looked for a confluence of evidence; that is, for consistent support for a causal relationship from different but complementary research designs that is supported by evidence of its biological plausibility.

Panel 5: study designs that are used in assessing causal effects of substance use

As noted in **panel 2**, governmental policies, and social and cultural factors, may affect some of the “harms” of substance use. For example, the risks of injecting drugs will be lower when clean injecting equipment is readily available, and information is provided on how to inject safely, than when needle sharing is common and levels of blood borne infections are high among older injectors. Similarly, young people who are arrested and imprisoned for illicit drug use may be exposed to other more drug-involved young people, and suffer the adverse effects of a criminal record that limits employment, study and other life possibilities.

The potential risks of substance use in young people

The unique changes, transitions and position of young people affect the potential impacts of substance use. We can broadly describe three ways (“triple risks”) in which this may occur. First, during adolescence and young adulthood acute intoxication and the short-term effects of regular, heavy use can have adverse health and social effects. Second, substance use initiated then can have longer term impacts by disrupting social transitions to adulthood and entrenching sustained, heavy or dependent substance use that affects health in adulthood. Third, substance use can have adverse effects on the offspring of young adults. We have summarised these in **Table 1** and indicated the strength of evidence for these associations being causal. **Webappendix B** provides greater detail on the studies described in this section.

The range of potential harms and the evidence differ between substances in multiple ways. There are: 1) qualitative differences in the harms of different substances (e.g. fatal overdoses vs. dependence); 2) differences in the life stage at which the harms occur (e.g. tobacco’s harms occur later in life while those of injecting drug use can occur much earlier); and 3) differences in the evidence on whether the harms are related to different types of substance use (e.g. case control studies vs longitudinal studies). A general limitation in this literature is that most evidence comes from high income countries. It is unclear to what extent the same social and health related outcomes would be seen in other countries and cultures.

Table 1 about here

1. Risks in adolescence and young adulthood

Polysubstance use

Young people who initiate early and regularly use one substance are much more likely to use others. In many high income countries, young people who begin using alcohol and tobacco in their mid-teens are much more likely to use cannabis; and early, regular cannabis users are more likely to use amphetamines, cocaine and heroin.³³ Debate continues about how best to explain these patterns of drug involvement. One explanation is that the sequence reflects the effects of shared risk factors.³⁴ This has most extensively been examined for cannabis, given that in high income countries it is the earliest illicit drug used (and the most common); adjustment for confounders attenuates but does not eliminate the relationship between regular cannabis use and the use of other illicit drugs.³⁴⁻³⁷

As noted in **paper 1**¹, in the World Mental Health Survey the order of initiation of substances varied greatly between countries.³⁸ No one sequence of substance initiation predicted progression to use of other substances. Rather, it was the extent of any kind of substance use that predicted later use of other substances.³⁸

Road traffic accidents and other unintentional injuries

Young people use alcohol and other drugs to experience their pleasurable intoxicating effects. Intoxication also increases risk taking, impairs judgment and psychomotor performance, and thereby increases the risk of injury if young people combine drug use with physical activities that include (but are not limited to) driving a car, swimming or climbing.

Alcohol use is a well-established cause of injury in young adults.³⁹ Case-control studies show a steep increase in the risk of road traffic accidents (RTA) with increasing alcohol intoxication; longitudinal studies show an increased risk of premature death from RTAs, in heavy-drinking young people, especially males⁴⁰.

There is less extensive but reasonable evidence that cannabis-impaired drivers have a higher risk of RTAs.⁴¹⁻⁴⁴ The contribution of other illicit drugs to accidental injury has been less well studied. Evidence of illicit drug use is found in persons killed in RTAs^{45, 46}, and people who use illicit drugs often report driving while intoxicated, but there have been very few case-control studies or experimental studies that have separated the effects of illicit drug use on accident risk from the riskier behavior of persons who use these drugs.^{46, 47} Cigarette smoking is associated with accidental injuries in young people, but it is unclear whether this association can be explained by confounding factors.⁴⁸

Violence

There is a consistent association between alcohol and some forms of illicit substance use⁴⁹⁻⁵¹ and violent behavior. Early studies attributed violence to the disinhibiting effects of substance use. More recently, however, studies have shown the need to consider the pharmacological effects of substance intoxication within a more complex network of biological, psychological and social factors. We discuss offending behaviour more generally below.

Affective and anxiety disorders

The risk of anxiety and affective disorders is elevated in individuals who use, or are dependent on cannabis, tobacco and alcohol.⁵²⁻⁵⁴ Cohort studies have also consistently demonstrated that use of these drugs are each strongly associated with later depression⁵⁴. It is unclear whether these associations⁵⁴ arise because: substance use predisposes individuals to

develop anxiety and depressive disorders; persons with these disorders use substances to alleviate their symptoms; or the associations arise from shared risk factors for substance use and these mental disorders.

A number of longitudinal studies have sought to disentangle these causal hypotheses (see **webappendix** for detail). In some cohort studies of young people who use alcohol the association was wholly explained by common risk factors^{55, 56}. One cohort found that symptoms of nicotine dependence influenced subsequent depressive symptoms, and common risk factors did not entirely explain this association.⁵⁷ A meta-analysis of cohort studies of cannabis use and later depression found a modest increase in depressive disorders among regular cannabis users⁵⁸, but most of these studies had not controlled for confounders, or excluded the possibility that depressed young people used cannabis to self-medicate.

Intentional self-harm and suicide

Heavy alcohol use is consistently associated with increased suicide risk in longitudinal studies, especially in young depressed males^{59, 60}. A causal role for alcohol is plausible because its intoxicating effects may increase impulsive suicidal behaviour.

Former and current smokers are more likely to report suicidal ideation than non-smokers,⁶¹ and regular smoking is associated with a greater risk of suicide attempts.⁶²⁻⁶⁴ Twin studies suggest that the association between nicotine dependence and suicidal behaviour is not explained by familial risk factors.⁶⁵

A small number of case-control, cohort studies and twin studies have reported associations between cannabis use and suicide in adolescents and young adults, with inconsistent findings.⁶⁶⁻⁷¹ One meta-analysis⁵⁸ concluded that the studies were too varied to meaningfully quantify risk and that most had not excluded reverse causation or controlled for confounding. There is poorer quality but very consistent evidence that suicide attempts and suicide deaths are highly elevated in people regularly using or dependent on other illicit drugs⁷²⁻⁷⁴ but these studies have not included adolescents.

Psychotic symptoms and psychotic disorders

An increasing number of studies have replicated associations between tobacco use and psychotic symptoms or disorder^{75, 76}, including genetic studies.⁷⁷ A recent meta-analysis found an increased risk of first-episode psychosis in cigarette smokers.⁷⁸

The evidence that heavy alcohol use causes psychosis is largely limited to case series of delirium tremens in severely alcohol dependent people,⁷⁹ or psychotic disorders in heavy alcohol users. These typically occur after decades of sustained heavy drinking.

A meta-analysis of cohort studies⁵⁸ found that people who used cannabis regularly had twice the odds of psychotic symptoms as peers who did not. Reverse causation was addressed in some of these studies by excluding cases who reported psychotic symptoms at baseline, or by statistically adjusting for pre-existing psychotic symptoms. The common cause hypothesis was harder to exclude because the association between cannabis use and psychosis was attenuated after adjustment for confounders, and no study assessed all confounders⁵⁸.

There is strong experimental evidence⁸⁰⁻⁸², confirmed by cohort studies of people using amphetamines^{83, 84}, that amphetamine use has strong psychotogenic properties. A causal relationship is supported by animal studies showing that amphetamine affects dopaminergic neurotransmission in ways which have been implicated in psychosis.⁸²

HIV and other infectious diseases

HIV infection is a risk for people who inject drugs, with the potential for rapid spread between injectors and to the wider community via sexual transmission.⁸⁵ Hepatitis B and C viruses (HBV and HCV) are more efficiently spread by unsafe injection than HIV^{86, 87}. HCV transmission is increasingly driven by injecting drug use. HBV is highly contagious through parenteral and sexual transmission routes. These risks can be substantially reduced by providing clean injecting equipment^{85, 88} (see **paper 3**⁸⁹ of this Series for a discussion of the evidence for these interventions).

Infectious disease can also be spread through unsafe sexual activity, which is associated with substance use in young people. For example, alcohol is linked to risky sexual behaviour; in sub-Saharan Africa, alcohol and risky sexual behaviour are associated with HIV.⁹⁰ The challenge is determining whether these associations are causal⁹¹ because there are many common risk factors for both sexual risk and substance use.

Fatal and non-fatal overdose

Overdose is causally related to substance use by definition. It is a risk for young people who use opioids, particularly if they also use CNS depressants such as alcohol and benzodiazepines. Fatal overdoses on stimulants are much rarer. It is difficult, if not impossible, to fatally overdose on cannabis.⁹²

Substance dependence

Regular substance users who develop tolerance to a drug may experience withdrawal symptoms when they stop^{93, 94} struggle to control their drug use, and meet criteria for dependence. As noted earlier, there is debate about whether the criteria used to diagnose drug dependence in adults apply to adolescents and young adults.

The risks of developing drug dependence vary with the drug and the route of administration. Nicotine and heroin are among the most addictive (in terms of the proportion of users who meet criteria for dependence, namely, 32% and 23% respectively). The dependence risks are lower for alcohol (15%), intranasal cocaine (15%), and cannabis (9%).⁹⁵

An early age of initiation to alcohol, tobacco, and cannabis use predicts a higher risk of substance use disorders. A plausible hypothesis is that early and regular use of drugs changes adolescents' brain function in ways that increase dependence risk.⁹⁶ A competing hypothesis is that early initiation is only an *indicator* of a higher pre-existing risk of problem drug use. The two hypotheses could both be true if early drug use acted on the brains of adolescents who are at higher risk of developing drug use disorders to increase that risk. In longitudinal studies, early initiation still predicts an increased risk of dependence but the association is usually attenuated after adjustment for confounders. Discordant twin studies have produced mixed results (see **webappendix B**).

Cognitive impairment

Given that significant brain development occurs in adolescence it is plausible that substance use in this period may affect synaptic pruning³⁰. Animal and f-MRI studies suggest that chronic nicotine exposure in adolescence affects attentional network functioning in the prefrontal cortex.⁹⁷ However, these studies have used very small samples and so are not powered or designed to control for confounding factors.^{97, 98} It is also unclear whether tobacco use results in cognitive deficits or whether people with cognitive deficits use nicotine to cope with cognitive dysfunctions.⁹⁸

Sustained heavy alcohol use throughout adulthood can produce severe cognitive impairment from cumulative neurotoxic effects of ethanol and nutritional deficiencies secondary to heavy drinking.⁹⁹ These disorders usually develop in mid to late adulthood after sustained heavy drinking over decades. It is unclear whether heavy alcohol use in adolescence can affect brain functioning in young adults in similar ways. Neuroimaging studies suggest that heavy drinking adolescents have more structural and functional brain abnormalities than low

drinking controls,⁹⁶ but it is difficult to determine whether these changes reflect pre-existing differences, the effects of heavy drinking or some combination of the two.

Case control studies have consistently found deficits in verbal learning, memory and attention in regular cannabis users, although it is unclear whether these cognitive functions fully recover after cessation of cannabis use and hence it is unclear whether these represent enduring changes in brain function.¹⁰⁰ A recent longitudinal study suggested that sustained daily cannabis use over several decades can produce substantial differences in cognitive performance that may not be wholly reversible.¹⁰¹ Reviews of functional imaging studies of long-term cannabis users^{102, 103} have concluded that we need larger, better-controlled studies before definitive conclusions can be drawn.

Educational attainment

Alcohol, tobacco and illicit drug use in adolescence are correlated with poor school performance and early school leaving. A plausible explanation is that regular drug and alcohol use impairs learning but this interpretation is complicated because adolescents who use these drugs have lower educational attainments and educational problems before using drugs. They also are much more likely to affiliate with peers who are substance users and out-of-school, and they often want to make a premature transition to adulthood.¹⁰⁴

A substantial part of the association may be explained by shared risk factors.^{105, 106} Nonetheless daily tobacco use prior to age 15 has been associated with poorer examination performance that persisted after controlling for confounders.¹⁰⁷ In longitudinal studies, cannabis use before the age of 15 predicts early school leaving, and this association persists after adjustment for confounders.¹⁰⁸⁻¹¹⁰ Twin studies suggest that the association is better explained by shared genetic and environmental risk factors for early cannabis use and early school leaving.¹¹¹⁻¹¹³ The association between early onset alcohol use and later educational attainment is less consistent after adjustment for confounders.¹¹⁰

Criminal activity

There have been many studies showing associations between substance use and criminal activity, particularly for illicit drugs.¹¹⁴ Among the potential explanations are:¹¹⁵ 1) the psychopharmacological hypothesis in which intoxication or withdrawal increase offending or young offenders use substances to facilitate offending); 2) an economic hypothesis that acquisitive crimes are committed to fund substance use; 3) a systemic hypothesis in which crime is generated by illicit drug markets; and 4) the common cause hypothesis in which

substance use and offending behavior reflect the effects of common causes. Reviews suggest common causes play a role but there is also evidence for all these hypotheses.¹¹⁵

2. Risks for role transitions and across the life course

Employment

Several longitudinal studies have demonstrated that early adolescent substance use is associated with reduced employment and stability, lower wages and poorer job satisfaction.¹¹⁶ Early initiation of use, use of illicit drugs and frequent substance use have been consistently associated with lower levels of employment, in men¹¹⁷ more than women.¹¹⁶

There appears to be a dose response relationship between substance use and employment, whereby heavy, frequent users of substances are more likely to have negative employment outcomes.¹¹⁸ It is plausible that this association is mediated by lower educational attainment among early adolescent substance users.

Financial independence

There is consistent evidence that heavy, early onset substance use in adolescence is associated with higher rates of financial dependence in adulthood, compared to young people with low rates of, or no substance use.¹¹⁷ For example, Fergusson et al^{67, 119} report higher rates of unemployment and welfare dependence in regular cannabis users, and these findings persisted even after adjustment for childhood, family and related factors. It is likely that the association between early onset substance use and decreased financial independence is closely linked to lower educational attainment and employment outcomes among early substance users. There has been some suggestion that early onset substance use increases the likelihood of adopting a lifestyle characterised by disengagement from social norms, such as completing an education and entering the workforce.¹¹⁷

Family formation

Substance use during adolescence may adversely affect interpersonal relationships and family formation for several reasons. Firstly, adolescent substance use may produce a ‘developmental lag’ whereby young people become entrenched in thinking and coping styles that impair their ability to form close interpersonal relationships. Secondly, the relationship between early substance use and risky sexual activity, early school dropout and higher rates

of unemployment may increase the likelihood of relationship failure. There is consistent evidence that cannabis use in young people is associated with greater relationship problems, including lower levels of relationship satisfaction,^{119, 120} reduced likelihood of marriage compared to non-users¹²¹ and reduced likelihood of residing with one's spouse.¹²⁰ There is some evidence among existing smokers that heavy and increasing tobacco use across early adolescence to adulthood is associated with greater problems in interpersonal relationships in early adulthood.¹²¹ Similarly, there is some evidence that binge drinkers who steadily increase their use across early adolescence are less likely to be married by age 23 than those who decrease their use over time.¹²¹

Physical health consequences

The physical health effects of substance use later in adult life are among the biggest contributors to health loss. These are the distal consequences of substance use initiated in adolescence and young adulthood, which persists into later life. It is in the later decades of life that the health consequences of tobacco smoking and alcohol use become apparent; the effects of illicit drug use occur earlier in adult life.¹²²

It is beyond the scope of this review to review the health consequences of long term tobacco and alcohol use. Tobacco smoking over decades is an important cause of multiple cancers, cardiovascular disease, chronic respiratory disease and a range of other non-communicable diseases¹²³. Similarly, heavy alcohol use over decades increases risks for a range of cancers, cardiovascular disease, cirrhosis of the liver, diabetes and a range of other non-communicable diseases¹²⁴.

There is less evidence on the long-term physical health effects of illicit substance use⁹¹. Stimulant drugs have been associated with cardiovascular problems¹²⁵ but the quality of studies is very poor. The general physical health of long term opioid and stimulant users is often very poor but almost no studies control for the confounding effects of other lifestyle risk factors, including alcohol and tobacco use.⁹¹

The strongest evidence for physical health consequences of long-term, regular cannabis smoking is for chronic bronchitis.¹²⁶ There is inconsistent evidence on long-term cannabis' effect on respiratory function¹²⁶. Recent reviews have concluded that there is still insufficient evidence on respiratory, or head and neck cancers.¹²⁷ Evidence for other long-terms health outcomes of cannabis is even weaker.

3. Risks for the next generation

There has been considerable research on the risks of substance use during pregnancy for the unborn baby. Maternal smoking during pregnancy is associated with poorer psychomotor development in childhood and poorer academic achievement and behavioural problems¹²⁸, independently of other variables.

Recent reviews on the effects of low or moderate alcohol consumption during pregnancy are inconclusive.¹²⁸ Very heavy or dependent drinking is associated with adverse impacts upon offspring and children via low birthweight and foetal alcohol spectrum disorder (FASD)¹²⁴.

There are inconsistent effects of pre-natal exposure to cannabis use on outcomes in babies and children. The causal interpretation of any such effects is weakened by the limited ability of these studies to control for the confounding effects of other drug use during pregnancy, poor parenting, and genetic factors.¹²⁶

There are also a range of other risks that are associated with heavy substance use by parents. These include exposure to trauma, less adaptive parenting styles, exposure to the substance use of parents and a range of other potentially negative events that may impact upon children. In the most part, the studies of this issue have been of parents with identified substance use problems, with little examination of the later effects of these events upon the child.¹²⁹

The increasing importance of substance use in the global health agenda for young people

As discussed in **paper 1**¹, substance use is a considerable contributor to health burden during adolescence and young adulthood in the Global Burden of Disease (GBD) studies. Substance use is increasing in many low and middle income countries. This is particularly the case for tobacco and alcohol, the health and social consequences of which may not be seen for some decades. There is explicit acknowledgement of the importance of addressing young people's substance use in key UN agendas. These include the Commission on Narcotic Drug's 2009 political declaration and plan of action to address "the world drug problem"¹³⁰, WHO's framework on tobacco control¹³¹ and WHO's global strategy to reduce harmful use of alcohol.¹³² **Paper 3**⁸⁹ provides a review of existing scientific evidence on a range of responses that have been used to address substance use in young people.

Our review has further considered the potential health and social consequences of young people's substance use using a life course perspective; these kinds of impacts are not as clearly reflected in GBD metrics. Our review of this evidence suggested that substance use may have impacts across many domains during adolescence and young adulthood. It can also have effects throughout adult life, via its impact on role transitions and milestones, and via the delayed health effects much later in life. These include a range of health and social outcomes that loom large on the international health and social agenda. We highlight several important examples of these below.

First, the sexual and reproductive health of young women has been emphasised¹³³ in the WHO Global Strategy for Women's, Children's and Adolescents' Health, 2016-2030.¹³⁴ Substance use may be an important risk factor for sexual risk taking, unintended pregnancy, sexually transmitted infections, and sexual violence. Very heavy substance use during pregnancy may affect the offspring of young women.

Second, young people who are heavily involved with substance use have higher risks of self-harm, suicide and mental disorders, such as depression and anxiety, and rarer but highly disabling disorders such as schizophrenia and other psychotic disorders (e.g. heavy amphetamine and cannabis use). Suicide and mental disorders feature prominently in the WHO's strategy regarding adolescents noted above¹³⁴, but also in the WHO's Mental Health Action Plan 2013-2020¹³⁵, as important causes of health burden in young people that require concerted attention.¹³⁶

Third, the recent UNAIDS Strategy 2016-2021¹³⁷ focuses on young people. As documented in this review, injecting drug use and heavy episodic alcohol use have both been linked with HIV risk. The magnitude of these risks varies geographically and with variations in HIV prevalence in the population and among people who inject drugs. Similarly, the extent to which knowledge, access and stigma affect risk taking, and access to risk reducing interventions varies widely across countries and cultures (as discussed in **paper 3**⁸⁹).

Research priorities

This review has highlighted major gaps in evidence. First, neuroscientific research suggests that young people may be especially vulnerable to the effects of substance use for multiple reasons.²³ However, much of this research in humans has not been of a sufficient standard to assess whether there are particularly elevated risks of substance use at this age (as opposed to at older ages). There is a pressing need for more sophisticated research designs, especially prospective studies, that integrate neuroimaging and genetics to understand relationships between adolescent substance use and adult health outcomes (e.g.¹³⁸). These studies should be done with a view to developing simpler assessment methods that can be used in low and middle income countries.

Second, many potential outcomes of substance use have been the subject of limited research. Third, the research that has been done has often used research designs poorly suited to assessing causality. Fourth, the geographic coverage of research is poor. This is a major obstacle to drawing of firm conclusions on causal impacts, given that many of the confounding factors involve social, cultural and interpersonal variables that vary widely between different countries and cultures. There is a clear need for well-conducted prospective studies of the health and psychosocial consequences of adolescent and young adult substance use in more diverse cultural and social settings than the small number of high income countries in which these studies have been done to date.

Finally, as has hopefully become evident in this paper, the impacts of the substance use on the unique transitions and changes that occur during this period may reach across the life course and affect the next generation. Research on substance use in young people to date has been short term and individually-focused. Future work should examine longer-term, social and intergenerational impacts of substance use during this important period of life.

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Conflict of interest

None to declare.

Author contributions

All authors had initial discussions about the content of the paper. WH and LD led the review, drafting and revision of the manuscript. ES and MW assisted with the literature searches and reviews. GP provided substantial feedback on the structure and logic of the manuscript. All authors contributed throughout the process to the critical review of the paper, reviewed particular sections in detail and commented on structure, provided substantial comment and approved the final version of the manuscript.

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Panel 1: Search strategy

We conducted a systematic review of reviews in Pubmed and Web of Science using search terms pertaining to substance use, young people, and health and social outcomes since 1990 (see **webappendix A** for search terms used). from 1990-present. We searched for reviews of substance use among those aged 10-24 years (see **paper 1** and <http://www.un.org/esa/socdev/documents/youth/fact-sheets/youth-definition.pdf>). EMBASE and Psycinfo were screened for material not indexed by Pubmed and Web of Science.

Peer-reviewed articles were initially assessed on the basis of title and abstracts, and those identified to be relevant were reviewed in full. The search strategy is included in **webappendix A**. Where relevant reviews were not available the addressed a particular health or social outcome, we conducted additional searches for good quality empirical studies and reviewed major books and grey literature reports e.g.¹³⁹.

Limitations of our search strategy

Although our search strategy was very wide in scope, it is important to acknowledge some limitations of the strategy. We did not search every database systematically, but concentrated on the largest two, with supplementary searches of others. Having said that, there is huge overlap between most of the remaining databases, such that it is unlikely that we missed any major systematic or other literature reviews of the potential consequences of substance use in young people. Additionally, where no reviews were located for a specific potential consequence of substance use, we supplemented this search with searches for empirical papers on the topic.

Second, we drew on grey literature sources including government reports and books, however we did not conduct a full systematic web search for these. To do so would have been an overwhelming task that was out of possibility for this review, however we did rely on more reputable sources for grey literature that should have capture the better conducted reviews of this topic, and contained more high quality reviews.

Third, we concentrated on reviews conducted since 1990. This may have missed reviews conducted in earlier years, however since we focused on a review of reviews approach, older empirical literature (i.e. pre-1990) is still included in many reviews, particularly the higher-quality research.

Finally, although not a limitation of our search strategy, it is important to note that there is considerable variation across studies in the way in which confounding is considered statistically, and in the range of variables considered as potential confounders, when empirical studies are considering whether there is support for a causal relationship between substance use and an outcome.

Panel 2: Cross-national differences in consequences of substance use?

- Nearly all the evidence on the correlates of substance use in young people has come from high income countries. This limits our understanding of the health and social consequences of substance use in young people as follows.
- **Varied societal experiences of adolescence:** The role, experience and length of the adolescent period varies widely between countries and cultures.
- **Variation in the roles of young women:** The social status and role of young women varies significantly between countries. Young women in some low and middle income countries have lower levels of education, and higher rates of teenage or very young adult marriage, and early pregnancy.
- **Variations in policy and social responses to substance use:** The legal and cultural response to substance use differs across countries. For example, risks of exposure to blood-borne viruses is far higher among young people who inject drugs in some countries than others¹⁴⁰ because preventive interventions such as needle and syringe programmes are not available,¹⁴¹⁻¹⁴³ and injecting drug use is stigmatised, increasing fear and limiting access to information and any services that do exist.

Panel 3: Social media, substance use and risk behaviour in young people

- In most countries there has been a dramatic increase in mobile technology coverage, with over 2 billion smartphones estimated to be in circulation in 2016¹⁴⁴.
- Large numbers of people access the internet using mobile devices¹⁴⁵, with young people the highest users of online and social media in high income countries¹⁴⁶. For example, 97% of Australian 8-17 year olds¹⁴⁵ use the internet and more than 90% own a mobile phone.¹⁴⁵ Most have email accounts, and interact via multiple apps such as Facebook, Instagram, Snapchat and Tumblr.
- New media can benefit young people by enhancing communication and social connectedness.¹⁴⁷
- But new media also carry risks: young people are especially susceptible to media because of their developing identities, the influence of peer relationships and their greater impulsivity.⁹⁷ New media also allow the rapid disseminate of messages – accurate or not - to large groups of young people.
- Young people may be especially susceptible to marketing of tobacco and alcohol via social media.^{148, 149}
- Risky substance use is associated with certain high risk forms of social media use such as “sexting”.^{150, 151}

Panel 4: Why substance use in young people differs from substance use in older adults

- Substance use in adolescents and young adults differs from that in older adults in a number of ways that may affect the nature and magnitude of any adverse effects of substance use.
- First, the same pattern of use may have different effects because of differences in physical development and in social and developmental contexts of adolescents, younger and older adults.
- Second, young people's inexperience might increase the adverse effects of acute intoxication because of a lack of understanding about doses required to obtain the desired effect. Older adults have more experience in titrating doses.
- Third, the shorter period of use means that young people are less likely than older adults to have entrenched, dependent patterns of substance use (although this can certainly occur). Young people's understanding of many of the symptoms of the "dependence syndrome" appears to differ from that of older adults (see **paper 1**), requiring more nuanced methods of assessment of dependence.
- Fourth, animal research suggests that substance use during adolescence may increase vulnerability to dependence²³ because of greater impacts on some areas of the brain (e.g.¹⁵²). This research has support from cross-sectional case-control studies in adolescent humans but needs to be strengthened by prospective study designs.
- For all of these reasons, we need evidence on the nature and magnitude of consequences of substance use in young people specifically.

Panel 5: Study designs used to examine associations between substance use and outcomes

- Causal inferences about the effects of any substance use require evidence that:
 - (1) substance use and the outcome are associated;
 - (2) reverse causation is unlikely; and
 - (3) shared risk factors do not provide a plausible explanation of the association.¹⁵³
- Some of the study designs that can be used to assess these issues are summarised below.
- **Case-control** and **prospective studies** can establish (1) and prospective studies can help to resolve (2) but (3) remains major challenge because experimentation is rarely ethically acceptable.
- **Statistical analyses of prospective studies** can adjust for differences between drug users and non-users.
Limitations: Studies may not have measured all confounders or measured them with error, and so are unable to fully control for their effects.
- **Genetic studies:** Identical and fraternal twin pairs who differ in drug use can be used to separate the effects of shared genetic and shared environmental risk factors.
Limitations: They cannot control for non-shared environmental risk factors e.g. peers.
- **Mendelian randomisation** uses genotypic information to test whether an observed relationship¹⁵⁴ is causal.
Limitations: It requires a genotype that is common, associated with exposure but not with the health outcome. Such genotypes may not exist.
- **Neuroimaging** studies can show correlations between drug use and changes in brain function in regions implicated in cognitive and emotional functioning.
Limitations: Most of these are small case-control studies so it is difficult to decide which is a cause, and which an effect of drug use.
- **Animal models** can assess the biological plausibility of causal relationships by studying the effects of drugs on the behavior and brains of peri-pubertal and adult animals.
Limitations: Uncertain relevance to human substance use because of interspecies differences in cognitive capacities and the inability to capture the social aspects of human adolescence.

Table 1: Evidence on the potential “triple risks” of substance use (during adolescence, across adulthood and for the next generation) for young people’s well-being

	Tobacco			Alcohol			Cannabis			Other illicit drugs*		
	Associated?	Likely causal?	Source	Associated?	Likely causal?	Source	Associated?	Likely causal?	Source	Associated?	Likely causal?	Source
Risks in adolescence and young adulthood												
<i>Mental and behavioural</i>												
Polysubstance use	✓	B	155	✓	B	153	✓	B	35-37, 155-157	✓	D	157
Substance dependence	✓	A	158-160	✓	A	50, 161-163	✓	A	156, 164, 165	✓	A	165
Depression	✓	B	146	✓	B	56, 166-168	✓	B	52, 53, 169	✓	C	169
Anxiety	✓	B	146, 170	✓	B	171	✓	B	58, 164, 169	✓	C	169
Psychotic symptoms/induced psychosis	✓	B	75, 76, 78	✓	B	146	✓	A	58, 82, 172	✓	A	80, 81, 169, 173
Violence	✗	-	-	✓	B	49-51	✓	D	144	✓	C	144
Risky sexual activity	✗	-	-	✓	B	161, 174, 175	✓	D		✓	C	176
Intentional self-harm	✗	-	-	✓	B	59, 60	✓	? B	66-69, 164, 177	✓	C	32
Suicide	✓	B	61-64	✓	B	50, 59, 161, 162, 177-179	✓	? B	66-69, 164, 177	✓	C	72-74
<i>Physical</i>												
Fatal overdose	✗	-	-	✓			✗	-	-	✓	A	
Road traffic accidents	✗	-	-	✓	A	50, 57, 161, 162	✓	A	41-44, 164, 180	✓	C	42, 44
Other accidental injuries	✓	D	48, 145	✓	A	124	✓	D	181		C	32
Sexually transmitted infections	✗	-	-	✓	? C	139, 182	✗	-	183	✓	B	32, 176
HIV, HCV, HBV	✗	-	-	✓	? B	182	✗	-	183	✓	A	176, 184, 185
Cognitive impairment	✓	E	97, 98	✓		99	✓	B	10, 186-188	✓	C	32
<i>Social and other</i>												
Lower educational attainment	✓	B	106, 107, 189	✓	B	161, 189	✓	B	104, 108-110, 157	✓	C	108, 157, 189
Criminal activity	✗	-	-	✓	? C	161	✓	? C		✓	? C	114, 115

* Other illicit drugs: opioids, amphetamines and/or cocaine.

\$ Opioids

% Cocaine

Amphetamines

Notes on codes used in this table

Presence or absence of effect

✗ This drug not appear to have a significant effect upon the outcome

✓ This outcome may be increased by the use of this drug

n/a not applicable

? There is insufficient data on this drug and this outcome to permit conclusions about the association between the two

Level of evidence

A Experimental or controlled evidence supports this finding

B Findings across cohorts, representative population-based

C Findings across cohorts of substance users

D Findings across cross-sectional studies, representative population-based, or case-control studies

E Cross-sectional associations among non-representative samples of substance users, case series suggesting outcome

Table 1 (continued)

	Tobacco			Alcohol			Cannabis			Other illicit drugs*		
	Associated?	Likely causal?	Source	Associated?	Likely causal?	Source	Associated ?	Likely causal?	Source	Associated?	Likely causal?	Source
Risks for social role transitions and across the life course												
<i>Social and other</i>												
Employment	✗	-	-	✗	-	-	✓	B	67, 171	✓	C	116, 118
Financial independence	✓	C	121	✓	C	121	✓	#	187	✓	C	
Family formation	✗	-	-	✓	C	39, 121	✓	D	187	✓	? C	
<i>Mental and behavioural</i>												
Substance dependence	✓	A	158-160	✓	A	95	✓	A	156, 164, 165	✓	A	95
Depression	✓	B	146	✓	B	56, 166-168	✓	B	52, 53	✓	C	169
Anxiety	✓	B	146, 170	✓	B	171	✓	C	58, 164, 190	✓	C	169
Psychotic symptoms/induced psychosis	✓	B	75, 76, 78	✓	B	146	✓	A	58, 82, 156, 172, 191	✓	A [#]	80, 81, 169, 173
Intentional self-harm/suicide	✗	-	-	✓	B	59, 60	✓	? B	187	✓	B	72-74
<i>Physical</i>												
Cardiovascular diseases	✓	A	123	✓	B	192	✓	C	186, 187	✓	C	32
Cancers	✓	A	123	✓	B	192	✓	C	186, 187	✓	C (injecting)	193
Chronic respiratory disease	✓	A	123	✗	-	-	✓	C	186, 187	✓	? C	194
Cirrhosis	✗	-	-	✓	B	128	✗	-	-	✓	B (injecting)	193
Diabetes and endocrine diseases	✗	-	-	✓	B	192	✗	-	-	✗	-	-
Other non-communicable diseases	✓	A	123	✓	B	192	✗	-	-	?	-	-
Skin and subcutaneous diseases	✗	-	-	✗	-	-	✗	-	-	✓	C (injecting)	195
Risks to the next generation												
Maternal reproductive health	✓	A	181	✓	B	48	✓	C	48, 156	✓	C	48, 156
Neonatal outcomes	✓	A	196	✓	B	197	✓	B	187	✓	C [%]	123
Child outcomes	✓	A	196, 198	?	B		✓	C	187	✓	C [%]	127

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